

Remarks

Claims 1-6 and 21-23 were pending in the subject application. By this Amendment, claims 3 and 23 have been amended, claims 1, 2, 4, 5, and 6 have been cancelled, and new claims 24-32 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 3 and 21-32 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

By this Amendment, the applicants have amended claim 3 and added claims 24-32. Support for these amendments can be found, for example, at page 3, lines 9-31, page 4, lines 1-7, page 6, lines 22-31, page 7, lines 1-16, page 14, lines 9-30, of the subject specification, and the claims as originally filed.

The Examiner has objected to the specification as failing to provide written support for the claimed subject matter. The Examiner asserts that the specification does not provide written support for claims directed to immunogenic compositions comprising RSV protein-type antigens. The applicants respectfully submit that the subject specification does provide a sufficient written description of the claimed subject matter to convey to one of ordinary skill in the art the inventors were in possession of the claimed subject matter at the time the application was filed. Submitted herewith for the Examiner's consideration are pages 21, 22, and 585 of the textbook "Fundamental Immunology" (Second Edition, Coleman, Lombard, and Sicard, Eds., Wm. C. Brown Publishers, 1992). As demonstrated by the scientific literature, the term "antigen" is recognized in the art to include "substances that can stimulate an immune response and, given the opportunity, react specifically by binding with the effector molecules (antibodies) and effector cells (lymphocytes) produced", as indicated at page 21, paragraph bridging first and second columns of the Fundamental Immunology text (emphasis added). Page 21, second column, lines 8-9, of the text states that "most antigens are proteins, but some contain carbohydrates, lipids, or nucleic acids." Furthermore, the term "antigen" is defined within the glossary of the Fundamental Immunology text as "any foreign material that can be specifically bound by antibody or T cell receptors" (emphasis added). The

applicants respectfully submit that the subject specification does not express an intent to impart a novel meaning to the term “antigen” and, thus, none should be read into the term.

Nonetheless, the Office Action appears to acknowledge that there is written support for the claimed invention in the originally filed claims. The claims as filed in the original specification are part of the disclosure. *In re Gardner*, 178 USPQ 149 (C.C.P.A. 1973). Furthermore, although the applicants submit that the claimed subject matter is disclosed in the specification, as the Examiner is undoubtedly aware, even if an application as originally filed contains a claim disclosing material not disclosed in the remainder of the specification, the applicants may amend the specification to include the claimed subject matter. *In re Benno*, 226 USPQ 683 (Fed. Cir. 1985). By this Amendment, the applicants have amended page 8 of the specification to include the subject matter recited in claims 1-6 of the application as originally filed. Accordingly, reconsideration and withdrawal of the objection to the specification is respectfully requested.

Claim 23 has been objected to under 37 C.F.R. §1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The applicants have amended claim 23 to delete the term “cocktail”. The term “plasmid DNA” finds antecedent basis in claim 21, from which claim 23 depends. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claim 4 has been rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The applicants respectfully submit that the recited mucosal vaccine is fully enabled by the subject specification. However, by this Amendment, the applicants have cancelled claim 4, rendering this rejection moot. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 3, 4, and 21-23 have been rejected under 35 U.S.C. §102(e) as being anticipated by, or in the alternative, under 35 U.S.C. §103(a) as obvious over Collins *et al.* (U.S. Patent No. 5,264,957). The applicants respectfully submit that the Collins *et al.* patent does not teach or suggest the immunogenic composition of the claimed invention. However, by this Amendment, the applicants have amended claim 3 to recite that the immunogenic composition comprises the M2 RSV antigen and at least three RSV antigens selected from the group consisting of F, G, M, SH, NS1,

NS2, N, and P RSV antigens. The Collins *et al.* patent does not teach or suggest the immunogenic composition as currently claimed. Claim 4 has been cancelled.

The Collins *et al.* patent discloses a composition containing one or more isolated polynucleotide molecules encoding an RSV genome or antigenome and N, P, L, and M2 (ORF1) proteins of RSV. Upon expression, the genome or antigenome and N, P, L, and M2(ORF1) combine to produce an infectious RSV particle (see column 3, lines 3-10 and 42-45). Thus, the Collins *et al.* patent does not teach an immunogenic composition comprising the M2 RSV antigen and at least three RSV antigens selected from the group consisting of F, G, M, SH, NS1, NS2, N, and P RSV antigens. The Collins *et al.* patent does not teach an immunogenic composition comprising the M2 RSV antigen, F RSV antigen, G RSV antigen, and at least one RSV antigens selected from the group consisting of M, SH, NS1, NS2, N, and P RSV antigens. Nor does the Collins *et al.* patent teach an immunogenic composition comprising all nine M2, F, G, M, SH, NS1, NS2, N, and P RSV antigens.

As the Examiner is aware, to be anticipatory under 35 U.S.C. §102, a reference must disclose within the four corners of the document each and every element and limitation contained in the rejected claim. *Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ 2d 1001, 1010 (Fed. Cir. 1991). The applicants respectfully submit that the Collins *et al.* patent does not teach or suggest every element of the applicants' claimed invention.

Furthermore, the applicants respectfully submit that the Collins *et al.* patent does not suggest the immunogenic composition as currently claimed. The Collins *et al.* patent states that the genome or antigenome of the recombinant RSV need only contain those genes or portions thereof necessary to render the viral or subviral particles encoded thereby infectious (see column 5, lines 52-60). The applicants respectfully submit that there is no suggestion or motivation in the cited reference that would lead a person skilled in the art to arrive at the subject invention. As a matter of law, a finding of obviousness is proper only when the prior art contains a suggestion or teaching of the claimed invention. The mere fact that the purported prior art could have been modified or applied in a manner to yield the applicants' invention would not have made the modification or application obvious unless the prior art references suggested the desirability of the modification. *In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984). Moreover, as expressed by the CAFC, to support a §103 rejection, "[b]oth the suggestion and the expectation of success must be founded in the prior art . . . ."

*In re Dow Chemical Co.*, *supra* at 1531. As shown by the foregoing remarks, the cited reference does not provide the suggestion to use the RSV antigens contained within the immunogenic compositions of the subject invention. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §102(e) and §103(a) is respectfully requested.

Claims 3 and 21-23 have been rejected under 35 U.S.C. §103(a) as being obvious over Collins *et al.* (PNAS, 1995, 92:11563-11567). Claim 4 has been rejected under 35 U.S.C. §103(a) as being obvious over Collins *et al.*, and further in view of Wright *et al.* (J. Infect. Dis., 2000, 182(5):1331-1342). Claims 3 and 21-23 have also been rejected under 35 U.S.C. §103(a) as being obvious over Domachowske (Clin. Microbiol. Rev., 1999, 12:298) in view of Hsu *et al.* (J. Gen. Virol., 1999, 80:1401-1405) and Simmons *et al.* (J. Immunol., 2001, 166(2):1106-1113). Claim 4 has also been rejected under 35 U.S.C. §103(a) as being obvious over Domachowske in view of Hsu and Simmons and further in view of Wyatt *et al.* (Vaccine, 1999, 18:392). The applicants respectfully submit that the cited references do not teach or suggest the subject invention. However, as indicated above, the applicants have amended claim 3 to recite that the immunogenic composition comprises the M2 RSV antigen and at least three RSV antigens selected from the group consisting of F, G, M, SH, NS1, NS2, N, and P RSV antigens. The cited references do not teach or suggest the immunogenic composition of the invention as presently claimed.

The Collins *et al.* publication describes an infectious human RSV produced by coexpression of five plasmid-borne cDNAs encoding the positive-sense version of the RSV genome and the N, P, L M2(ORF1) proteins. Therefore, the Collins *et al.* publication does not teach an immunogenic composition comprising the M2 RSV antigen and at least three RSV antigens selected from the group consisting of F, G, M, SH, NS1, NS2, N, and P RSV antigens, as recited in claim 3. There is also no suggestion to substitute the L RSV protein for F, G, M, SH, NS1, or NS2 RSV proteins, for example. In fact, it was observed that RSV was not produced if any of the five plasmids were omitted (see abstract of Collins *et al.*). Furthermore, the NS1, NS2, and SH RSV proteins are only mentioned within the context of ablating or reducing their expression within the RSV genome, or to yield mutant forms of the proteins.

The Office Action indicates that the Domachowske publication teaches the RSV M2, N, F, SH, and NS2 proteins are targets for CTL (cytotoxic T lymphocytes) in humans. However, the

applicants note that the Domachowske publication also indicates that the protective effects associated with a vaccine-induced immune response to N and M2 are short-lived, and that G protein fails to induce a CTL response. The Hsu *et al.* publication describes induction of RSV-specific neutralizing antibodies and CTL after immunization with a mixture of peptides consisting of a B-cell mimotope, a T-helper epitope (SH:45-60), and a CTL epitope linked to a fusion (F) peptide (F/M2:81-95), that were comparable to those induced by the peptides alone. The applicants respectfully submit that the Hsu *et al.* publication merely indicates that a synergistic effect on protection against RSV was observed after immunization with synthetic peptides bearing epitopes that induce antibody and CTL responses. At page 1404, the paragraph bridging first and second columns, the Hsu *et al.* publication points out that immunization with purified F protein results in enhanced pulmonary pathology following RSV challenge, and priming with G protein of RSV resulted in eosinophilia and atypical lung disease. “Immunization with whole proteins or with inactivated vaccines may not always result in the induction of appropriate responses, since these vaccine preparations may not be formulated in a way to allow antigen processing and presentation via the MHC class I pathway” (see page 1404, column 2, lines 5-9, of Hsu *et al.*). Furthermore, the Hsu *et al.* publication does not suggest the combination of four or more RSV antigens, since the desired induction of both antibody and CTL response can be achieved with only a “triple cocktail” of a T-helper epitope (SH:45-60), a CTL epitope linked to a fusion peptide, and a B-cell mimotope. No motivation is provided by the cited reference or the Examiner to modify the synthetic peptides of the Hsu *et al.* publication to arrive at the immunogenic compositions of the present invention. An assertion of obviousness without the required suggestion or expectation of success in the prior art is tantamount to using applicants’ disclosure to reconstruct the prior art references to arrive at the subject invention. This was specifically recognized by the CCPA in *In re Spinnoble*, 56 CCPA 823, 160 USPQ 237, 243 (1969):

The Court must be ever alert not to read obviousness into an invention on the basis of the applicant's own statements; that is we must review the prior art without reading into that art appellant's teachings. *In re Murray*, 46 CCPA 905, 268 F.2d 226, 112 USPQ 364 (1959); *In re Sprock*, 49 CCPA 1039, 301 F.2d 686, 133 USPQ 360 (1962). The issue, then, is whether the teachings of the prior art would, in and of themselves and without the benefits of appellant's disclosure, make the invention as a whole, obvious. *In re Leonor*, 55 CCPA 1198, 395 F.2d 801, 158 USPQ 20 (1968). (Emphasis in original)

Here, it is only the applicants' disclosure that teaches the desirability of an immunogenic composition comprising the recited antigens.

As indicated above, claim 4 has been cancelled, rendering moot the rejections under §103(a) as obvious over Collins *et al.*, and further in view of Wright *et al.*, and Domachowske in view of Hsu and Simmons and further in view of Wyatt *et al.*

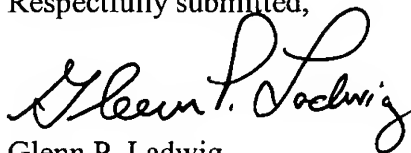
Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachment: Pages 21, 22, and 585 of the textbook "Fundamental Immunology"



# FUNDAMENTAL IMMUNOLOGY

SECOND EDITION

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immunity integrates phagocytes with other effector cells and places primary emphasis on certain classes of lymphocytes (described later) for specific cellular immunity.

### *Integration of Humoral and Cellular Immunity*

For a time, an intense conflict existed between advocates of the two theories. However, around the turn of the century, it became increasingly obvious that both cellular and humoral factors were involved in acquired immunity. For example, Metchnikoff had observed that microorganisms were more effectively engulfed in immunized than in nonimmunized animals. In addition, Wright and Douglas, in 1903, demonstrated that immune serum contained a factor that adhered to microorganisms (similar to those used to immunize the animal), making them more easily engulfed by phagocytes. Cells and humoral factors thus appeared capable of cooperation in defending the body.

Later, it became apparent that nonspecific immunity, present at birth, might be mediated, in part, by humoral factors in body secretions and, in part, by phagocytes. On the other hand, specific immunity, acquired after birth by exposure to disease or through immunization, might be mediated by specific antibodies and by specific cells. Today, it is known that immune responses involve interactions of both humoral and cellular immunity.

### **Antigens**

Invasive viruses, bacteria, fungi, protozoa, worms, cancer cells, foreign tissues, and worn out cells can exhibit, produce, or release nonself substances known as antigens. **Antigens** are substances that can stimulate an immune response and, given the opportunity, react specifically by binding with the effector molecules (antibodies) and effector cells (lymphocytes) produced. (For further discussion of antigens see chapter 3, Effectors of Humoral Immunity.) This definition of an antigen focuses on two important properties that were formally identified by Obermayer and Pick in 1903, namely, **immunogenicity** (the capacity to stimulate the formation of antibodies) and **specificity** (the ability to react specifically with these antibodies). This latter property means that in a humoral immune response an

antigen reacts selectively with its corresponding antibody and not with any of the variety of antibodies formed in response to other antigens. Similarly, in a cell-mediated immune response, an antigen induces selective activation of some, but not all, effector cells.

### *Nature of Antigens*

Most antigens are proteins, but some contain carbohydrates, lipids, or nucleic acids. Some antigens are more **immunogenic**, or capable of eliciting an immune response, than others. An antigen, such as a protein, can possess a number of small chemical groupings that are called **antigenic-determinant groups**. Any one determinant group, under appropriate conditions, can stimulate the formation of a particular kind of antibody molecule or effector cell. Thus, a pure protein antigen might give rise to many distinct antibodies and effector cells.

Immunogenicity and specificity of antigens can be altered by chemical treatment. For example, attaching various chemical groups to protein antigens can cause different antibodies to be formed. In 1921 Landsteiner coined the term **hapten** to describe these specific chemical groups that are, by themselves, incapable of stimulating antibody formation but, when associated with proteins, are capable of doing so.

### *Tolerogens*

Antigens do not always exhibit immunogenicity or evoke antibody formation, however. In some instances, an antigen presented at one concentration might induce *specific immunological unresponsiveness*; or **tolerance**, while at another concentration it might promote immunity. An antigen that induces tolerance is referred to as a **tolerogen**.

The notion of immunological tolerance was proposed in 1944 by Medawar and Burnet and earned them the 1960 Nobel Prize. One important manifestation of tolerance occurs during fetal development. Since an individual's immune system does not normally react against self-components, Burnet suggested that fetal immunocytes were deleted by contact with their specific autoantigens. This process, called *clonal deletion*, supposedly led to removal of immunocytes that would react against self-antigens. In this manner, an individual became tolerant to self-antigens. It has since

become clear, however, that mammals possess all the genetic information necessary to react immunologically against self-constituents, although this rarely occurs. Nevertheless, autoimmune responses do occur under certain circumstances. (See chapter 10, Immune Tolerance and Suppression, and chapter 16, Autoimmunity, for further discussions.)

### Histocompatibility Antigens

Immunological tolerance has become an exciting and active area of research that is especially relevant to the problems of tissue and organ transplantation. Unless the tissue proposed for transplantation is antigenically identical to that of the intended recipient, the recipient's immune system attempts to reject it. The antigens of tissues that are responsible for evoking immunological responses against grafts are called histocompatibility antigens. They are encoded by genes known as histocompatibility genes, which collectively constitute a **major histocompatibility complex (MHC)**. Thus, MHC products present markers of individual identity. MHC products on human leukocyte surfaces, known as human leukocyte-associated (HLA) antigens have been used extensively in identifying potential donors for transplants. In addition to serving as surface markers for tissue typing, HLA antigens are involved in critical regulatory interactions. Chapter 7, Histocompatibility Systems, explores this topic in greater depth.

## Antibodies

### Nature of Antibodies

The term **antibody** refers to a spectrum of proteins that are formed in response to an antigen and that react specifically with that antigen. Antibodies belong to a group of proteins known as **immunoglobulins (Igs)**. There are five major classes of immunoglobulins (*IgG*, *IgM*, *IgA*, *IgD*, and *IgE*), each with specialized properties (see chapter 3, Effectors of Humoral Immunity). These are easily distinguished on the basis of their characteristic heavy polypeptide chains.

**IgG** is the most common class and plays a critical role in most humoral responses. All antibody molecules, regardless of class, have a basic four-chain structure consisting of two identical **light (L)** and two

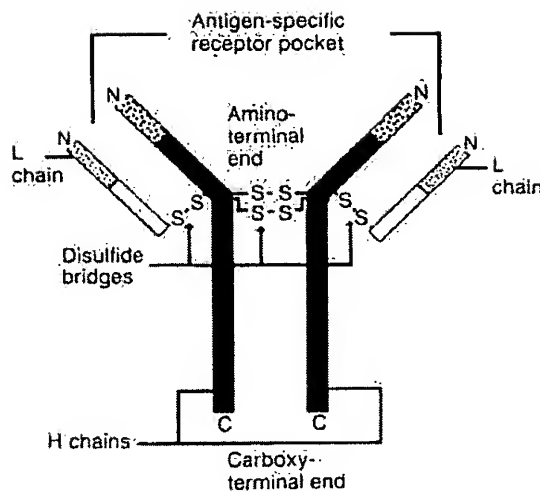


FIGURE 1.7 General structure of an antibody molecule. The basic structure of an antibody molecule is represented by IgG. This molecule has two heavy (H) and two light (L) polypeptide chains that are linked to each other as depicted. Constant regions of these chains are shown in solid color (white or black), while the variable regions are stippled. The variable regions are responsible for the specificity shown for a particular antigen. In addition, carbohydrate moieties (not depicted) are attached to the H chains at several sites (see chapter 3 for additional details).

identical **heavy (H) polypeptide chains** (fig. 1.7). Portions of both L and H chains vary uniquely in different antibody molecules. *Variable regions* in each L and H chain form a *specific receptor* or "*pocket*," which is genetically programmed and *complementary* to a *specific antigenic determinant*. Thus, two identical receptor sites for binding specific antigenic determinants are present on each four-chain structure. The *variable sequence* of amino acids at amino-terminal ends of the randomly paired L and H chains is essentially responsible for the antibody specificity expressed. The specificity of an antibody molecule is, therefore, a product of gene expression. Antibody specificity refers to the ability of an antibody to discriminate between two antigenic determinants. The structure of antibody molecules was elucidated in the late 1950s by **Porter, Edelman**, and others. The value of these studies, which provided the basis for a more thorough understanding of the chemistry of antibody specificity and the mechanism of antigen-antibody binding, was recognized by the award of the 1972 Nobel Prize in Physiology to Porter and Edelman.

**AIDS-Related Complex** Loosely defined group of conditions marked by the display of multiple systemic infections—but in the absence of clinically defined AIDS.

**ALL** Acute lymphocytic leukemia.

**Allele** Single form of a gene at a given locus that controls a particular characteristic.

**Allelic Exclusion** Phenotypic expression of only one of the two allelic forms of a gene present in heterozygous cells.

**Allergen** Environmental antigen that stimulates allergic reactions that are expressed as immediate (Type I) hypersensitivity responses mediated by IgE.

**Allergy** Hypersensitive state acquired through exposure to a particular allergen.

**Allogeneic** Genetic dissimilarity among members of the same species.

**Allograft** Graft of cells, tissues, or organs between allogeneic individuals. Also known as a homograft.

**Allotypic Determinants** Determinants found as allelic variants of antigens, such as immunoglobulin molecules, which may be found in some but not all members of a species.

**$\alpha$ -Fetoprotein** Antigen that is normally expressed by fetal tissues but abnormally occurs in association with certain forms of cancer. It is one of several substances, known as oncofetal antigens, that are used as tumor markers in adults.

**$\alpha$ -Macroglobulin** Serum protein of maternal origin that suppresses cell-mediated immune responsiveness against fetal antigens.

**Alternative Complement Pathway** Antibody-independent cytolytic pathway of serum proteins that includes complement components C3-C9 of the classical complement pathway and several other independent factors (Factors B, D, H, I, P). This pathway can be activated by microbial products. It is also known as the properdin pathway.

**A<sub>m</sub> Marker** Allotypic marker that appears in one of two forms on IgA light chains of some individuals.

**Amebocyte** Phagocytic immune effector cell of many invertebrate species. This represents an early

(phylogenetically primitive?) nonspecific effector of cellular immunity.

**Anamnestic Reaction** Immune response involving immunological memory and heightened responsiveness upon exposure to a previously encountered antigen.

**Anaphylatoxins** C3a, C4a, C5a, which are released into blood following activation of complement. These can cause mast cell degranulation and histamine release capable of producing the symptoms of anaphylaxis.

**Anaphylaxis** Reaction characterized by vasodilation and smooth muscle contractions, possibly leading to hypotension, bronchoconstriction, and urticaria. It is an immediate (Type I) hypersensitivity reaction that follows exposure to an antigen in sensitized individuals that is induced by the release of mediators from IgE-coated mast cells.

**Angiogenesis** Process of blood vessel formation.

**Anterior Chamber-Associated Immune Deviation** Special case of selective suppression of delayed (Type IV) hypersensitivity reactions within the eye. Its occurrence can lead to adverse effects of infections on the visual system.

**Antibody** Serum protein formed in response to a single antigenic determinant, which is capable of binding specifically with the antigenic determinant or epitope that induced its formation.

**Antibody-Dependent Cellular Cytotoxicity** Form of cytotoxicity reaction in which target cells become coated with antibody and subsequently are lysed by leukocytes bearing Fc receptors.

**Antigen** Any foreign material that can be specifically bound by antibody or T cell receptors.

**Antigen-Binding Site** That part of an antibody molecule, or T cell receptor molecule, that binds to an antigenic determinant. It is also known as the paratope.

**Antigen-Dependent Differentiation** Differentiation of mature T or B cells into expressive elements of cellular or humoral immunity that is triggered by exposure to antigen.

#### **Antigen-Independent Differentiation**

Differentiation of mature T and B cells from lymphocyte precursors. This process might begin in the fetal liver or adult bone marrow but continues in specific microenvironments where commitments are made to become mature, antigen-responsive T (thymus) or B cells (bursa or bone marrow).

**Antigen-Presenting Cell** Cell that processes and presents antigen, in association with MHC molecules, to lymphocytes such as T<sub>H</sub> cells.

**Antigenic Determinant** Single antigenic site, or epitope, on a molecule that reacts with antibody or T cell antigen receptor.

**Antigenic Modulation** Loss or change in expression of surface antigens displayed by infectious agents and cancer cells.

**Antilymphocyte Serum** Serum containing antibodies against lymphocytes that can be used to produce immune suppression.

**Antinuclear Antibody** Diagnostic feature of individuals afflicted with LE. Its presence is usually visualized by immunofluorescence microscopy.

**Antioncogene** A gene whose absence (or failure to be expressed normally) leads to cellular transformation or tumor expression. Also known as tumor suppressor gene.

**Antiserum** Serum from an immunized individual that contains antibodies against a particular antigen.

**APC** Antigen-presenting cell.

**ARC** AIDS-related complex.

**Arthus Reaction** Reaction appearing as a rash induced by deposition of immune complexes in cutaneous capillaries following repeated presentation of antigen.

**Ataxia Telangiectasia** Immune deficiency disorder characterized by uncoordinated muscular movement and vascular dilation. This developmental disorder occurs before hemopoietic stem cell maturation and leads to a progressive depression of cellular and humoral immunity and to defects in neural and endocrine function as well.

**Atopy** Genetically determined, IgE-mediated, immediate (Type I) hypersensitivity response to an allergen.